UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,449	10/06/2003	Liwen Huang	1438.01	4490

26698 7590 08/09/2005

MYRIAD GENETICS INC.
INTELLECUTAL PROPERTY DEPARTMENT
320 WAKARA WAY
SALT LAKE CITY, UT 84108

EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/680,449	HUANG ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.000

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II (Claims 16–20) in the reply filed on May 20, 2005, is acknowledged. The traversal is on the ground(s) that no serious burden would be imposed on the examiner as the claims drawn to the process for altering gene expression by RNA interference using a shared, common, or universal target sequence, and a kit for performing the process do not have separate status in the art and do not require a different field of search, since both groups are classified in class 514, subclass 44. Applicants further argue that all pending claims pertain to the same concept of altering gene expression and that if the disclosed method is not in the prior art the kits for practicing the method are not in the prior art. Therefore, a search for altering gene expression by RNA interference using a universal target sequence would suffice for all the pending claims.

This is not found persuasive for the following reasons. First, Class 514, subclass 44 contains multiple inventions, which require further sorting and analysis according to specific keywords to identify relevant art. Second, classification searching does not reflect the entire search burden since in the biotech arts keyword-based searches of patent and non-patent literature in separate databases is essential to identify relevant art. Finally, applicants are reminded that a full search of patent and non-patent literature involves both a search of the literature and a consideration of the hits, as to each structural limitation and method step. While a search of the method for altering gene expression may reveal some references that would also relate to the kit for practicing

the method, a search of the method would not necessarily provide all the references relating to the kit. Moreover, applicants have not elected the method. Thus, the requirement is still deemed proper and is therefore made FINAL.

Status of the Application

Claims 1–20 are pending. Claims 1–15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 20, 2005.

Location of the Application

The location of the application has changed. The instant application has been docketed to Examiner Louis V. Wollenberger.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16–20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 16 and dependent Claim 17 recite "A kit for practicing the method of Claim 2,...". However, as set forth above, Claim 2 has been

withdrawn from consideration as being drawn to a non-elected invention. Thus, the recitation "the method of Claim 2" presently conveys no meaning to Claim 16. Claim 18 and dependent claims 19 and 20 are similarly rejected since they recite "the method of Claim 1," also withdrawn as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16–18 and 20 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hirashima et al. (1986) *PNAS* 83:7726–7730.

Claim 16 is drawn to a kit comprising in a compartmentalized carrier: 1) a plurality of expression vectors each being capable of directing the expression of a chimeric RNA transcript that has a subject RNA operably linked to a universal target

RNA; and 2) a universal interfering RNA targeting said universal target RNA. Claim 17 limits Claim 16 by stating that the plurality of expression vectors are arranged in an addressable array on a solid support. Claim 18 is drawn to a kit comprising in a compartmentalized carrier: 1) a plurality of target cells or organisms each expressing a chimeric RNA transcript that has a subject RNA operably linked to a universal target RNA; and 2) a universal interfering RNA targeting said universal target RNA. Claim 19 limits Claim 18 by stating that the plurality of target cells or organisms are selected from the group consisting of plant cells, plant tissues, plant seeds, nematode cells, plants and nematodes. Claim 20 limits claim 18 by stating that the target cells or organisms are arranged in an addressable array on a solid support.

For purposes of examination of the instant claims, the ordinary meaning of the term "compartmentalized" has been applied since applicants do not specifically define the term in the specification. The Cambridge International Dictionary of English defines the term "compartmentalize" as a verb "to separate something into parts and not allow those parts to mix together." The term "carrier" is taken to mean "a container for carrying," (Merriam-Webster Online)—e.g., a bottle or a plastic tray.

Furthermore, applicant is advised that the use of the phrase "being capable of" in connection with "expression vectors" in Claim 16 describes a variety of different bacterial and mammalian expression vectors, i.e., even empty plasmids, commonly used in the art of recombinant DNA, for cloning and expressing gene fusions, all of which are capable of directing expression of a chimeric RNA transcript.

With regard to Claim 17, applicants define addressable arrays on pages 60, 61, 64, and 65, and state that such arrays may consist of at least 2 or more distinct addresses. The examiner submits that 2 separate vessels, bottles, containers, culture flasks, or test tubes containing different subject RNAs, or cells or organisms expressing different subject RNAs defines an addressable array within the meaning of Claims 17 and 20. Support for this interpretation is found on page 65 of the instant application, which states that "For macroarrays of transgenic organisms, arrays can be produced by arranging containers suitable for the culture of such organisms, in a regular configuration with defined addresses. Such arrays may consist of test tubes arranged in a rack, or culture vessels (e.g., flower pots) arranged on a tray, and such arrays may comprise 2, 3, 4, 6, 12, 18, 24, 48, 96, 120, 180, 240, 480, 960 or more transgenic organisms."

Finally, it is noted that the instant application states (page 16) that: "The term 'subject RNA,' as used herein, refers to an RNA whose cellular concentration is to be altered, manipulated or reduced, or knocked down, by the action of an interfering RNA targeting the universal target RNA, but not the subject RNA." The use of the term "refers to" indicates that a "subject RNA" is not to be narrowly limited to or defined as a particular species of RNA but is to be regarded, or classified within a general category or group. Thus, for purposes of this examination, the universal target and subject RNAs may be separate and distinct genes or simply different sequences or different yet contiguous regions within the same gene.

Hirashima et al. teach an antisense (micRNA) that inhibits viral infection, replication, and expression in *E. coli.* Specifically, the authors disclose a 19-base micRNA (pMIC-D5; page 7729; Fig. 1 and Table 2) encompassing the Shine-Dalgarno sequence common to bacteriophages SP, Qβ, and GA that exerted potent immune effects on all three phages. Thus, a single (universal interfering) antisense RNA was shown to target multiple (subject) RNAs all of which were operably linked to the same (universal) target RNA: the Shine-Dalgarno sequence. In this reference, each phage is considered to represent a different expression vector within the scope of that recited in Claim 16, since each phage is capable of expressing a chimeric RNA that has a different subject RNA (the SP, Qβ, and GA phage genomes) operably linked to a common target RNA (the Shine-Dalgarno sequence). The pMIC-D5 19-base micRNA is considered to represent the universal interfering RNA recited in Claims 16 and 18. The limitations of Claim 18 are met since the assays conducted by Hiroshima et al. involved the infection of *E. coli* cells with a plurality of expression vectors expressing a chimeric RNA that have different subject RNAs (the SP, Qβ, and GA phage genomes) operably linked to a common target RNA (the Shine-Dalgarno sequence). The limitations of Claims 16 and 18 that the components be in a compartmentalized carrier, and of Claims 17 and 20 that the plurality of vectors or cells or organisms are arranged in an addressable array on a solid support are also met because although Hiroshima et al. do not explicitly state that the samples were in "a compartmentalized carrier" or arranged in "an addressable array," it would have been expected and otherwise obvious to keep the vectors and cells in separate containers (i.e., an addressable array) to prevent the

targets from comingling on the benchtop. It is a matter of standard laboratory practice to conduct side-by-side tests on samples that are in separate vessels. Moreover, at least two samples are tested in the Hiroshima et al. report, which defines an array as stated in the instant application on page 65. Moreover, prior to beginning and after completing the experiment and the various vectors and cells, it would be expected and otherwise obvious for the investigators to keep the various samples in different containers on a shelf or in a rack, for example, any of which fit the ordinary definition of a compartmentalized carrier, as explained above.

*****

Claims 18–20 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 103(a) as obvious over Sijen et al. (2001) *Cell* 107:465–476 (cited in applicants' IDS).

Sijen et al. teach a method for inducing transitive RNAi in *Caenorhabditis elegans*, a nematode (pp.467–468). At the start (page 466 and Fig. 1), the authors provide a working model for transitive RNAi, which shows how "trigger" interfering dsRNAs targeting downstream target sequences induce secondary RNAi of upstream sequences. The authors pose the question "Could siRNA-Primed Copying of Target RNAs by an RNADirected RNA Polymerase Contribute to RNAi?" (Fig. 1 legend). The authors propose that "antisense siRNAs that have annealed to a ssRNA target might be elongated by RdRP to produce longer stretches of dsRNA." The authors further state that "The model in Figure 1C leads to a number of testable predictions; in particular, we would expect to observe a population of secondary siRNAs after RdRP-mediated

synthesis of duplex RNAs followed by cleavage by RNaseIII/DICER activity. These secondary triggers would be derived primarily from sequences upstream of the initial trigger region on the target mRNA and would be expected to induce a secondary RNA interference reaction directed to any homologous target RNA" (page 466).

Sijen et al. test this hypothesis using a transgenic line of *C elegans* expressing two different green fluorescent protein reporter constructs: *myo-3::gfp-lacZ* and *myo-3::gfp* (Fig 3, page 467–8). The gfp reporter expression constructs, designated pSAK2 and pSAK4, schematically illustrated in Fig 3A, are said to be independently driven by the *myo-3* promoter (page 468). It is noted by the examiner that the constructs *myo-3::gfp* and *myo-3::gfp-lacZ* are not native to *C elegans*; thus, it is expected that the expression cassettes were originally produced *in vitro* by cloning into standard expression vectors using conventional recombinant DNA techniques. Thus, the expression vectors pSAK2 and pSAK4 meet the limitations of Claim 16 as being capable of expressing a chimeric RNA transcript.

Sijen et al. further show that gfp expression is silenced in transgenic nematodes containing both the pSAK2 and pSAK4 constructs when the nematodes are exposed to dsRNA targeting the *lacZ* region (Fig. 3). Thus, Sijen et al. disclose an interfering RNA targeting a target RNA operably linked to a subject RNA. These results inform the skilled artisan that, in *C elegans,* target RNAs act as templates for secondary silencing of adjacent, upstream sequences. Because the gfp gene serves merely as convenient reporter in this assay and is not a determinant of the silencing effect, the skilled artisan would recognize that different reporters or genes (i.e., different subject RNAs) linked to

the same target RNA would undergo suppression in the same manner as that observed for gfp. The authors go so far as to test the positional requirements of the effect stating (page 468) that "Of two *lacZ* segments tested, a trigger that was located just 3' to the *gfp*::*lacZ* junction (*ds-lacZU*) was most potent in the transitive RNAi assay, producing reduction of mitochondrial GFP to background in 60% of deletion and wild-type alleles, while a dsRNA trigger located further downstream (*ds-lacZL*) produced a more modest effect (reduction of GFP in 28% of cells) (Figure 3 and data not shown)."

Claims 18–20 are anticipated by Sijen et al. in view of their teachings in column 2, page 468, where they disclose wild-type, homozygous, and heterozygous nematodes within the scope of the instant claims. They state, "In-frame deletion alleles of *unc-22* and *unc-52* provide a useful genetic tool: these alleles each produce proteins that lose a fraction of the coding region (658 amino acids for *unc-22*(*st528*); 150 for *unc-52*(*ra511*)) but retain full wild-type function. As expected, dsRNAs corresponding to the deleted regions produced strong gene-specific RNAi effects in wild-type animals, but no effect in animals homozygous for the corresponding deletion alleles. The test for transitive RNAi in each case consists of introducing these trigger RNAs into animals carrying both wild-type and mutant alleles. In each case, we found a strong transitive RNAi effect: heterozygotes exhibited interference with both deletion and wild-type alleles. These experiments demonstrate that transitive RNAi is not limited to transgene targets, but can also target physiological expression of cellular genes."

The limitations of Claim 19 and 20 are met since, as explained above in the previous rejection, because although Sijen et al. do not explicitly state that the samples

were in "a compartmentalized carrier" or arranged in "an addressable array," it would have been expected and otherwise obvious to keep the organisms in separate vessels (i.e., an addressable array) to prevent the organisms from comingling. It is a matter of standard laboratory practice to conduct side-by-side tests on separate samples that are in separate vessels (i.e., an addressable array). Moreover, at least two samples are tested by Sijen et al, which falls within the meaning of an array. Furthermore, because the expression constructs are expressed by organisms—namely, nematodes—the limitations of 19 are met.

*****

Conclusion

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information.

It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

LVW August 4, 2005

Louis V. Wollenberger, Ph.D.
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER
1635